Complete Summary

GUIDELINE TITLE

Practice parameter: initiation of treatment for Parkinson´s disease: an evidence-based review.

BIBLIOGRAPHIC SOURCE(S)

Miyasaki JM, Martin W, Suchowersky O, Weiner WJ, Lang AE. Practice parameter: initiation of treatment for Parkinson's disease: an evidence-based review: Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2002 Jan 8;58(1):11-7. [31 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Parkinson´s disease

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Neurology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To review the available evidence concerning the initiation of treatment for Parkinson´s disease and to provide recommendations based on this evidence
- To address the following specific questions:
    - Does selegiline offer neuroprotection?
    - What is the best agent with which to initiate symptomatic treatment in de novo Parkinson's disease?
    - Is there a benefit of sustained release levodopa over immediate-release levodopa?

TARGET POPULATION

De novo (previously untreated) patients with Parkinson´s disease (PD)

INTERVENTIONS AND PRACTICES CONSIDERED

Treatment/Assessment of Therapeutic Efficacy

1. Levodopa (sustained-release or immediate-release)
2. Dopamine agonists (pramipexole, ropinirole and cabergoline)
3. Selegiline

MAJOR OUTCOMES CONSIDERED

- Risk of developing disability requiring levodopa therapy
- Motor function as reflected by Unified Parkinson's Disease Rating Scale (UPDRS) scores
- Changes in Activities of Daily Living (ADL) scores
- Rate of motor complications (wearing off, dyskinesia, on-off motor fluctuations)
- Quality of life
- Adverse effects of medications used to treat Parkinson´s disease
- Mortality rates in Parkinson´s disease patients being treated with selegiline (compared to mortality rates in non-selegiline treatment groups)

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The English literature between 1966 and 2000 was searched using MEDLINE, EMBASE, and the Cochrane Library. The key words used were: early or de novo Parkinson´s disease, human trials, double-blind method. Only articles that fulfilled class I or class II evidence were included. Since the effectiveness of levodopa and dopamine agonists compared with placebo in the treatment of early Parkinson´s disease is established, the guideline developers focused on studies comparing dopamine agonists with levodopa. Articles were identified using the generic term dopamine agonist or specific drug names (bromocriptine, cabergoline, pergolide, lisuride, pramipexole, ropinirole). Similarly, for controlled-release versus regular

or immediate-release levodopa, comparator only studies were used. In examining the neuroprotective effects of selegiline, only studies in de novo patients were evaluated. Studies utilizing selegiline in patients already receiving symptomatic therapy were included to address the safety of selegiline in this patient population.

NUMBER OF SOURCE DOCUMENTS

Neuroprotective effects of selegiline: 2 articles

Safety of selegiline: 3 articles

Dopamine agonists as monotherapy in de novo Parkinson's disease patients: 3 articles

Immediate- versus sustained-release levodopa: 1 article

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Ratings for the Quality of the Evidence:

- Class I. Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population. The following are required: (a) primary outcome(s) is/are clearly defined; (b) exclusion/inclusion criteria are defined; (c) adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias; (d) relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.
- Class II. Prospective matched group cohort study in a representative population with masked outcome assessment that meets a-d above OR a randomized controlled trial in a representative population that lacks one criteria a through d.
- Class III. All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment.
- Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion.

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The author panel critically assesses the topic through analysis of the medical literature. The abstracts and articles are each reviewed by several panel members and excluded or included as appropriate to the clinical question being assessed. All articles included in the literature review are rated based on their quality. The subsequent recommendations are weighted based on the quality of the evidence on which they are based. Data are abstracted and formulated into a draft guideline with specific recommendations.

For this guideline. the results of the literature search were as follows:

- 38 articles for selegiline were identified, two of which addressed the issue of neuroprotection. Articles were rejected for the following reasons: 13 utilized selegiline as adjunctive treatment, 5 examined symptomatic benefit only, 5 examined nonmotoric effects of selegiline, 3 were repeat publications, 3 were interim reports, 3 were commentaries on ongoing research, and 1 was a review, not a meta-analysis.
- Three articles addressing safety of selegiline in Parkinson´s disease were reviewed.
- Seventy-eight articles for dopamine agonists used as monotherapy in de novo patients were identified; only three were long-term studies (2 years or longer) fulfilling American Academy of Neurology (AAN) criteria for level I or II evidence. Articles were rejected for the following reasons: 36 utilized the dopamine agonist as adjunctive treatment, 19 did not use a levodopa (active) control, 5 utilized nonmotor endpoints, 5 provided level IV evidence, 4 were open-label studies, 3 were interim reports with subsequent publication of the complete study, 2 were repeat publications, 1 was a review article, not a meta-analysis, and 1 was a report of human toxicity.
- Only one article was found that examined immediate-release versus sustained-release levodopa in a trial fulfilling American Academy of Neurology (AAN) criteria for level II evidence.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Definitions for the Strength of the Recommendations

- A. Established as effective, ineffective or harmful for the given condition in the specified population. Level A rating requires at least one convincing class I study or at least two consistent, convincing class II studies.
- B. Probably effective, ineffective or harmful for the given condition in the specified population. Level B rating requires at least one convincing class II study or at least three consistent class III studies.
- C. Possibly effective, ineffective or harmful for the given condition in the specified population. Level C rating requires at least two convincing and consistent class III studies.
- U. Data inadequate or conflicting; given current knowledge, treatment is unproven.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Before approving a draft guideline, the committee circulates it to outside experts, physician, and patient organizations, other American Academy of Neurology sections and committees, volunteer American Academy of Neurology member reviewers, and other specialists (e.g., ethics specialists, legal counsel) when pertinent. All comments are reviewed by the committee and the author panel. Working with the panel facilitator, the author panel summarizes and addresses each comment received.

Before being published as an American Academy of Neurology practice guideline, the draft must receive approval from its sponsoring subcommittee, the American Academy of Neurology Practice Committee, and the American Academy of Neurology Board of Directors. Approval by the Board of Directors signals the adoption of the guideline as the official position of the American Academy of Neurology.

This guideline was approved by the Quality Standards Subcommittee on August 11, 2001, by the Practice Committee on October 17, 2001, and by the American Academy of Neurology Board of Directors on October 20, 2001.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Definitions of the strength of the recommendations (A, B, C, U) and classification of the evidence (Class I through Class IV) are provided at the end of the "Major Recommendations" field.

Selegiline. What is the role of selegiline in the treatment of early Parkinson´s disease (PD)?

Conclusions

Selegiline has mild symptomatic benefit (class II). There is no convincing clinical evidence for neuroprotective benefit with selegiline (class II). There is no convincing evidence for increased mortality with selegiline whether it is given in combination with levodopa or as monotherapy (class II).

Recommendations for Patients with Parkinson's Disease Who Require Symptomatic Treatment

Initial symptomatic treatment of patients with Parkinson's disease with selegiline in order to confer mild, symptomatic benefit prior to the institution of dopaminergic therapy may be considered (level A, class II evidence).

There is insufficient evidence to recommend the use of selegiline to confer neuroprotection in patients with Parkinson's disease (level U).

Initiating dopaminergic treatment. When symptomatic therapy is required, does levodopa or a dopamine agonist offer best control of motor symptoms?

Conclusions

Levodopa, cabergoline, ropinirole, and pramipexole are effective in ameliorating motor and activities of daily living disability in patients with Parkinson's disease who require dopaminergic therapy.

Levodopa is more effective than cabergoline, ropinirole, and pramipexole in treating the motor and activities of daily living features of Parkinson's disease.

Initiating dopaminergic treatment. When symptomatic therapy is required, does levodopa or a dopamine agonist offer the most favorable long-term complication profile?

Conclusions

Cabergoline, ropinirole, and pramipexole treatment of Parkinson's disease patients requiring dopaminergic therapy results in fewer motor complications (wearing off, dyskinesias, on-off motor fluctuations) than levodopa treatment after 2.5 years of follow-up.

Cabergoline, ropinirole, and pramipexole treatment of Parkinson's disease patients requiring dopaminergic therapy is associated with more frequent adverse events including hallucinations, somnolence, and edema than levodopa therapy.

Recommendations

In patients with Parkinson's disease who require the initiation of dopaminergic treatment, either levodopa or a dopamine agonist may be used. The choice depends on the relative impact of improving motor disability (better with levodopa) compared with the lessening of motor complications (better with dopamine agonists) for each individual patient with Parkinson's disease (level A, class I and class II evidence).

Sustained-release versus immediate release levodopa: When initiating levodopa therapy, which formulation should be used—immediate-release or sustained-release levodopa?

Conclusions

When initiating therapy with levodopa, there is no difference in the rate of motor complications between immediate-release levodopa and sustained-release levodopa.

Recommendations

For patients with Parkinson's disease in whom levodopa treatment is being instituted, either an immediate-release or sustained-release preparation may be considered (level B, class II evidence).

Definitions:

Ratings for the Quality of the Evidence

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- Class II. Prospective matched group cohort study in a representative population with masked outcome assessment that meets a through d above OR a randomized controlled trial in a representative population that lacks one criteria a through d.
- Class III. All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment.
- Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion.

Definitions for the Strength of the Recommendations

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- C. Possibly effective, ineffective or harmful for the given condition in the specified population. Level C rating requires at least two convincing and consistent class III studies.
- U. Data inadequate or conflicting; given current knowledge, treatment is unproven.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate selection of medications in the treatment of de novo Parkinson's disease patients in order to obtain an optimal reduction of parkinsonism with a minimal risk of long-term side effects

POTENTIAL HARMS

Side Effects of Medication

- Levodopa. Early use of levodopa might predispose patients to develop long-term motor complications such as wearing off, dyskinesia, dystonia, and on-off phenomenon. Some studies have reported incidence of these complications as high as 80% in young patients and 44% in older patients after 5 years of levodopa treatment. The frequency of dyskinesias alone is reported to range between. 30 and 80% after 5 to 7 years of levodopa use.
- Dopamine agonists (cabergoline, ropinirole, pramipexole). These agents result in fewer motor complications than levodopa but are associated with more frequent adverse effects including hallucinations, somnolence, and edema.
- Selegiline. One study raised the issue of excess mortality in patients receiving selegiline with levodopa (76/271) compared with those receiving levodopa alone (44/249), However, other studies have failed to show convincing evidence for increased mortality with selegiline whether it is given alone or in combination.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The American Academy of Neurology recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

The guideline is published in the journal Neurology, posted on the Academy's Web site, sent to all American Academy of Neurology members in an annual mailing, announced in the Academy's newsletter, submitted to the Agency for Healthcare Research and Quality (AHRQ) National Guideline Clearinghouse™ and listed in the American Medical Association Practice Parameter Directory and CD-ROM.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2002 Jan 8

GUIDELINE DEVELOPER(S)

American Academy of Neurology - Medical Specialty Society

SOURCE(S) OF FUNDING

American Academy of Neurology (AAN)

GUIDELINE COMMITTEE

Quality Standards Subcommittee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Authors: J.M. Miyasaki, MD; W. Martin, MD; O. Suchowersky, MD; W.J. Weiner, MD; and A.E. Lang, MD

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

It updates a previously issued version: Quality Standards Subcommittee of the American Academy of Neurology. Practice parameters: initial therapy of Parkinson´s disease (summary statement). Neurology 1993;43:1296–7.

GUIDELINE AVAILABILITY

Electronic copies: Available from the American Academy of Neurology (AAN) Web site.

Print copies: Available from the AAN Member Services Center, (800) 879-1960, or from AAN, 1080 Montreal Avenue, St. Paul, MN 55116.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- AAN guideline development process. St. Paul (MN): American Academy of Neurology.

Electronic copies: Available from the American Academy of Neurology (AAN) Web site.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on February 12, 2002. The information was verified by the guideline developer on September 5, 2003.

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